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Catastrophe and homeostasis

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ABSTRACT

The seasonal change in the duration of the night time release of melatonin is responsible for activating the hypothalamic gonadtrophin-releasing hormone (GnRH) pulse generator in seasonal breeding animals. Paul Mullen and I considered that it might also be responsible for the activation of the child's GnRH pulse generator at the onset of human puberty. The real conundrum, though, is why this should happen when it does. Homeostasis, which explains how the body is able to maintain itself, cannot explain why things change. Our reasoning was that in any homeostatic state, there might exist two systems in disequilibrium, which eventually collide to create the 'catastrophe' of change. Our research showed that a constant daily output of melatonin throughout life was in disequilibrium with increasing body mass throughout childhood. These two systems permit the progressive decrease in the circulating concentration of melatonin in the growing child until it drops below a critical threshold, which then creates the 'catastrophe' of puberty. Catastrophe is destined to overthrow the established order, whereas homeostasis protects it. Catastrophe is always a transient moment that is rapidly supplanted by the re-imposition of homeostasis. Copyright © 2010 John Wiley & Sons, Ltd.

A year of revolution and counter-revolution

Paul and I first met when he was a newly qualified doctor and I was a medical student at the Middlesex Hospital in London. We were drawn together by common interests in food, wine, movies, theatre, literature and music. But we also connected through our somewhat unusual (at least for medics) political beliefs. Paul was involved with the May Day Manifesto and International Socialism, which also gave him the opportunity to court Liz, who was an active militant. The tactic was clearly successful since she is now his wife. Prior to studying medicine, I had been at the Sorbonne where I studied philosophy with Jean-Francois Lyotard. This had introduced me to the movement 'Socialisme ou Barbarie' where Lyotard wrote political missives under the pseudonym of François Laborde. So when Paul and I met, the common thread of our political beliefs was

that Marxism was not dead, instead it had been expropriated by the Communist Party, which had turned it into a bureaucratic machine of state even more oppressive than the capitalist system it denounced. I doubt, however, if our shared political beliefs would have cemented our friendship to such an intense degree but for the fact that we met following a year of political drama.

Nineteen sixty-eight was a year of revolution and counter-revolution. In February, the Vietcong launched their Tet offensive against the US forces in South Vietnam, and, for a brief moment, it looked as if the might of the US military was going to be defeated by a people's militia. This was followed by a series of extraordinary events in France, the sacking of Henri Langlois from the Cinémathèque française leading to the new wave directors (Truffaut, Godard, Chabrol, and others) boycotting the Cannes Film Festival. This was accompanied by student unrest at the University of Nanterre, which finally erupted in the May student uprising against the infamous riot police, the Compagnies Républicaines de Sécurité (CRS), in the streets of Paris, where the cobbles were used as missiles against the forces of the government. Eventually, the unions joined the students, and there was a general strike. The government of General de Gaulle seemed set to fall (Figure 1). The unrest in Paris was echoed by what was happening in

Figure 1: A poster from May 1968 showing student revolutionary demonstrators at bottom left, and the image of a baton bearing CRS counter revolutionary defender of the established order at top left

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Prague, where Alexander Dubjec was proclaiming 'socialism with a human face' and the emancipation of Czechoslovakia from the yoke of the Soviet Empire. On the other side of the Atlantic, the black medallists at the summer Olympics raised their gloved fists in a defiant Black Power salute against white America. The anti-war movement in the USA reached its crescendo with the violent student protest outside the Democratic Convention in Chicago where the demonstrators battled with Mayor Daley's police. But revolution was followed by counter revolution. The Vietcong were beaten back by superior US military forces. General de Gaulle summoned General Massu and his army stationed in Germany to suppress the student revolt in Paris. Bobby Kennedy and Martin Luther King were assassinated. Nixon won the Presidential election. The Soviet tanks rolled in to Czechoslovakia to suppress the Prague Spring. The only lasting achievement of 1968 was that Henri Langlois was reinstated at the Cinémathèque française!

Among leftist libertarians, the disillusion which followed was profound. Some found solace in drugs, some in therapy, some in new age movements and some in classical reform politics. Paul and I found solace in science, where, without fully realising it at the time, we metamorphosed the struggle of revolution against counter-revolution into that of catastrophe against homeostasis.

Years of research

The agent of our scientific research was N acetyl 5 methoxy tryptamine (melatonin). Melatonin is synthesised in the pineal gland by two enzymes: the first, N acetyl transferase (NAT), converts serotonin (5HT) to N acetyl serotonin (NAS) and the second, hydroxy indole O methyl transferase (HIOMT), converts NAS to melatonin (Figure 2A). The importance of this is twofold: (1) melatonin can only be produced in the pineal gland because HIOMT is only found in the pineal gland and nowhere else in the body, and (2) melatonin is principally synthesised by the pineal gland during the hours of darkness because NAT is activated by darkness and inhibited by light (Figures 2B,C).

This creates a central role for melatonin in the four clock system that underlies biological rhythm. Nights are longer in winter than in summer, so it follows that the duration of the night time release of melatonin is longer in winter than in summer (Figure 3A). It is the seasonal change in the duration of the night time secretion of melatonin which is responsible for seasonal breeding in all seasonal breeding animals. The interlocking four clocks are: (1) an environmental yearly clock providing a change in the length of daylight at different seasons of the year; (2) a pineal 24-hour clock providing a change in the duration of the night time release of melatonin, which is dependent on the seasonal changes of the yearly clock; (3) a hypothalamic hourly clock providing the pulsatile release of gonadtrophin-releasing hormone (GnRH) for about 6 minutes every hour, which is activated or inactivated depending on the duration of night time release of melatonin from the 24-hour pineal clock; and (4) a gonadal monthly clock, or oestrus

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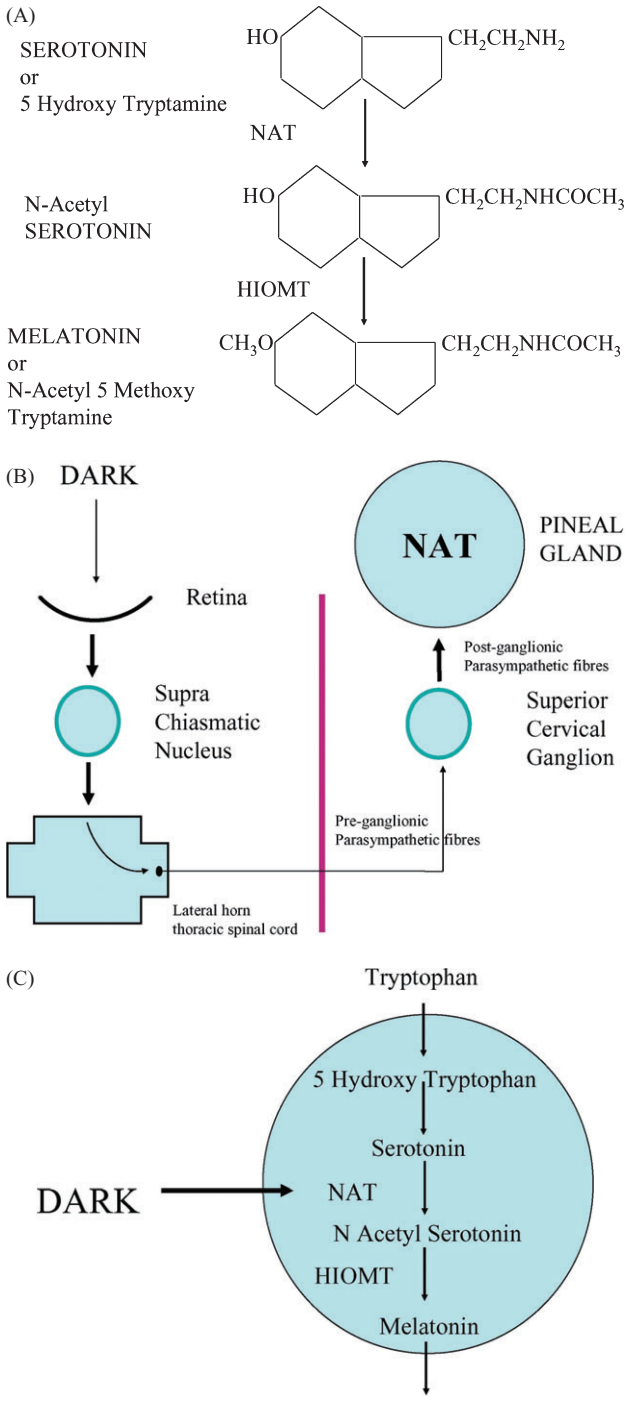

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Figure 2: Melatonin is released from the pineal gland at night. (A) The synthesis of melatonin from serotonin via two pineal enzymes (1) N acetyl transferase (NAT) and (2) hydroxy indole O methyl transferase (HIOMT). (B) The nervous pathway from retina to pineal for the activation of the enzyme NAT. The pathway exits the CNS at the lateral horn of the thoracic spinal cord to travel as parasympathetic fibres alongside blood vessels until it reaches the pineal gland. (C) NAT is the rate limiting step in the synthesis of melatonin from dietary tryptophan within the pineal gland. It is activated by darkness and inhibited by light, ensuring that melatonin is secreted principally during the night. HIOMT is a pineal specific enzyme, ensuring that circulating melatonin comes exclusively from the pineal gland

cycle or menstrual clock, which is dependant on the activation of pituitary follicle-stimulating hormone (FSH) and luteinising hormone (LH), which, in its turn, is dependent on the activation of the hourly hypothalamic GnRH clock (Figure 3B).

There were several reasons why Paul and I were fascinated by melatonin. The obvious was that disturbance of biological rhythms might explain disturbances of mind and body, such as seasonal affective disorder, or unexplained infertility being caused by a permanent melatonin winter. Another reason was because we had stumbled upon an exquisitely sensitive and specific method for measuring melatonin and its metabolites using gas chromatography mass spectrometry (GCMS). As a consequence, I infiltrated myself into the Department of Reproductive Physiology at St. Bartholomew's Hospital Medical College, where I commandeered the GCMS laboratory for the assay of melatonin, while Paul set off for the Institute of Psychiatry where he commandeered the sleep laboratory to sample patients and volunteers during the day and night. The research publications poured forth (Smith et al., 1976; Mullen and Silman, 1977; Wilson et al., 1977; Mullen et al., 1978; Carter, Laude, Smith, Leone, Hooper, et al., 1979; Carter, Laude, Smith, Leone, Silman, et al., 1979; Hooper, Silman, Leone, Finnie, Carter, Grudzinskas, et al., 1979; Hooper, Silman, Leone, Finnie, Carter, Savage, et al.1979; Leone, Silman, Hooper, Carter, et al., 1979; Leone, Silman, Hooper, Finnie, et al., 1979; Linsell et al., 1979; Mullen et al., 1979; Silman et al., 1979; Smith et al., 1979).

Why things change

The principal reason why we were studying melatonin, however, was because we had created a surrogate for our battle between revolution and counter-revolution by transferring it to the struggle between catastrophe and homeostasis.

The concept of homeostasis was articulated by Claude Bernard (1957, translated edition) in the 1860s, when he proposed that the survival of an organism

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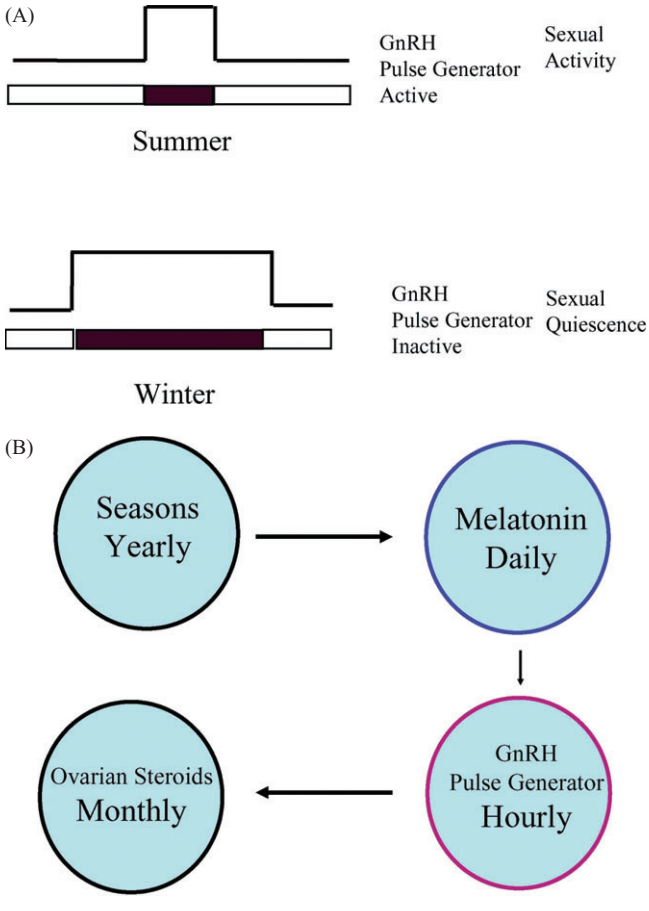

Figure 3: Seasonal breeding is controlled via melatonin. (A) On the left is a schematic representation of the 24-hour light/dark cycle in summer (top) and winter (bottom) with the accompanying rise of circulating melatonin at night, the duration of which is shorter in summer than in winter. It is the seasonal change in the duration of the night time release of melatonin that activates or inactivates the hypothalamic gonadtrophin-releasing hormone (GnRH) pulse generator, thereby controlling seasonal breeding in all seasonal breeding animals. (B) The four biological clocks: (1) top left, the yearly environmental clock where the length of light and dark changes according to the season of the year; (2) top right, the 24-hour pineal clock where melatonin is secreted at night; (3) bottom right, the hourly hypothalamic clock where GnRH is secreted for 6 minutes every hour; and (4) the ovarian monthly clock or oestrus/menstrual cycle

depended on the maintenance or constancy of its internal environment, the *milieu intérieur*, against the fluctuations or onslaughts of its external environment, the *milieu extérieur*. Cannon, in the 1920s, coined the phrase *homeostasis* to raise Bernard's vision to an all encompassing unifying concept of human physiology (Wolfe et al., 2000). Homeostasis has succeeded in becoming the overarching

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explanation for all diseases and their treatment. 'The physician fulfils his role by helping nature to make effective (…) adjustments of the organism that has become deranged or in need of reinforcement' (Cannon, 1928).

The predominance of homeostasis as the overriding explanation for everything that happens in medicine can be illustrated by a simple homeostatic positive/negative feedback loop. Take, for example, the pituitary hormone adrenocorticotrophic hormone (ACTH), which stimulates the secretion of cortisol from the adrenal cortex, which in its turn inhibits ACTH (Figure 4A). The inhibition of ACTH decreases the secretion of cortisol, which in turn stimulates ACTH (Figure 4B). And so it goes on, with a rhythmic, but polar opposite, increase and decrease in the circulating levels of ACTH and cortisol around a constant mean (Figure 4C). Cushing's disease, which is a disruption of this homeostatic feedback loop, can be caused by a pituitary adenoma releasing ACTH, which cannot be downregulated by cortisol. This, in its turn, leads to a pathological unregulated increase in cortisol, which, if unchecked, will end in death. The cure is to remove the pituitary adenoma and/or downregulate cortisol to normal levels by some other means. So, to rephrase Cannon, we can define disease as the disruption of homeostatic mechanisms, and therapy as their restoration or replacement.

Homeostasis, or the maintenance of the body's status quo, cannot, however, be the unifying concept of human physiology. The body does not stay the same throughout life. The body goes through a series of necessary changes. It starts as a fertilised ovum, it then becomes an embryo, then a foetus, then (after delivery) a neonate, then a baby, then an infant, then a pre-pubescent child, then a post-pubescent adolescent, then so on unto death. In other words, the one thing that *never* happens is that the body stays the same. So, the unanswered question in any unifying concept of human physiology is not how the body stays the same, but why it changes. Though homeostasis is the explanation for how things stay the same, catastrophe might help us explain why things change.

As originally conceived by Rene Thom, catastrophe theory is a complex mathematical model for explaining discontinuities in physical systems. 'Catastrophes are abrupt changes arising as a sudden response of a system to a smooth change in external conditions' (Arnol'd VI, 1992). Paul and I, as non-mathematicians, decided to translate this principle into a truly simple concept, almost as simple as homeostasis itself, in order to explain the discontinuities in biological systems. The key to understanding how this might work is to accept that homeostasis is the guiding principle in any particular state, such as the state of being a pre-pubescent child or the state of being a post-pubescent adolescent, but that within these homeostatic states systems can exist in slight disequilibrium. So one can conjecture that in the state of being a pre-pubescent child, homeostatic mechanisms are operating as described by Bernard and Cannon, but there are (at least) two systems which are set on a slow course to collision. Nothing happens to upset this pre-pubescent state until the two systems collide, at which point

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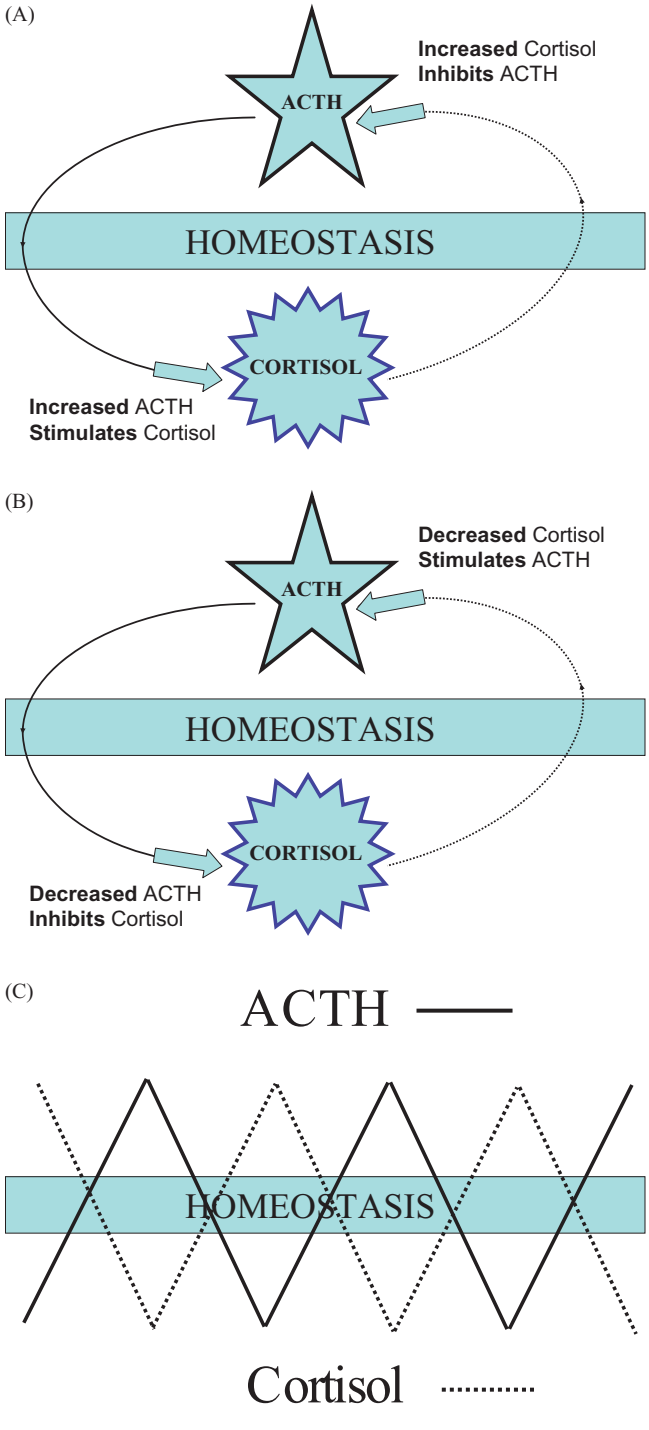

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Figure 4: The homeostatic feedback loop for ACTH and cortisol. (A) The secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland stimulates the secretion of cortisol from the adrenal gland. The increased secretion of cortisol from the adrenal gland inhibits the secretion of ACTH from the pituitary gland. (B) The decreased secretion of ACTH from the pituitary gland inhibits the secretion of cortisol from the adrenal gland. The decreased secretion of cortisol from the adrenal gland stimulates the secretion of ACTH from the pituitary gland. (C) The homeostatic positive/negative feedback loop in Figure 4A and B cause the circulating levels of ACTH and cortisol to rise and fall inversely around a constant mean

the collision (catastrophe) gives rise to the new state of the post-pubescent adolescent.

The catastrophe of puberty

So what two systems in the pre-pubescent state are destined to collide? And what happens at the moment of collision? And why does this explain the new state of the post-pubescent adult?

During the pre-pubescent state, the child's hypothalamic GnRH pulse generator is inactive, and, thus, there are low levels of pituitary FSH and LH and therefore low levels of the gonadal steroids oestrogen and testosterone. The transition from pre-pubescence to pubescence occurs as the consequence of a single event, namely the activation of the GnRH pulse generator; this means the pulsatile release of hypothalamic GnRH for approx six minutes every hour. Why does this event occur? Why is the GnRH pulse generator dormant during pre-pubescence and activated at about the age of 10? The answer cannot simply be hypothalamic maturation, because the GnRH pulse generator is active in late foetal life, but then suppressed until puberty. Nor can it be anything to do with homeostasis, because homeostasis is concerned with keeping things the same.

The premise for our answer lay in the supposition that there might be two systems in disequilibrium during pre-pubescence which, when they finally collide at about the age of 10, activate the GnRH pulse generator and explain the 'catastrophe' of puberty – the conversion from the pre-pubescent homeostatic state to the post-pubescent homeostatic state. We measured the urinary metabolites of melatonin, principally 6 sulphatoxy melatonin, throughout all ages of life and discovered that the 24-hour output of melatonin from the pineal gland (as determined by the 24-hour urinary output of its metabolite) remained constant throughout life. In other words, pineal output was not related to body size, being the same for a 3-year old child as for a 30-year old adult. This led us to the second system, which is body mass. A child grows, and therefore the body mass of a 3-year old is much less than that of a 30-year old adult. Hence, given the constant daily output of melatonin from the pineal gland, the circulating concentration is

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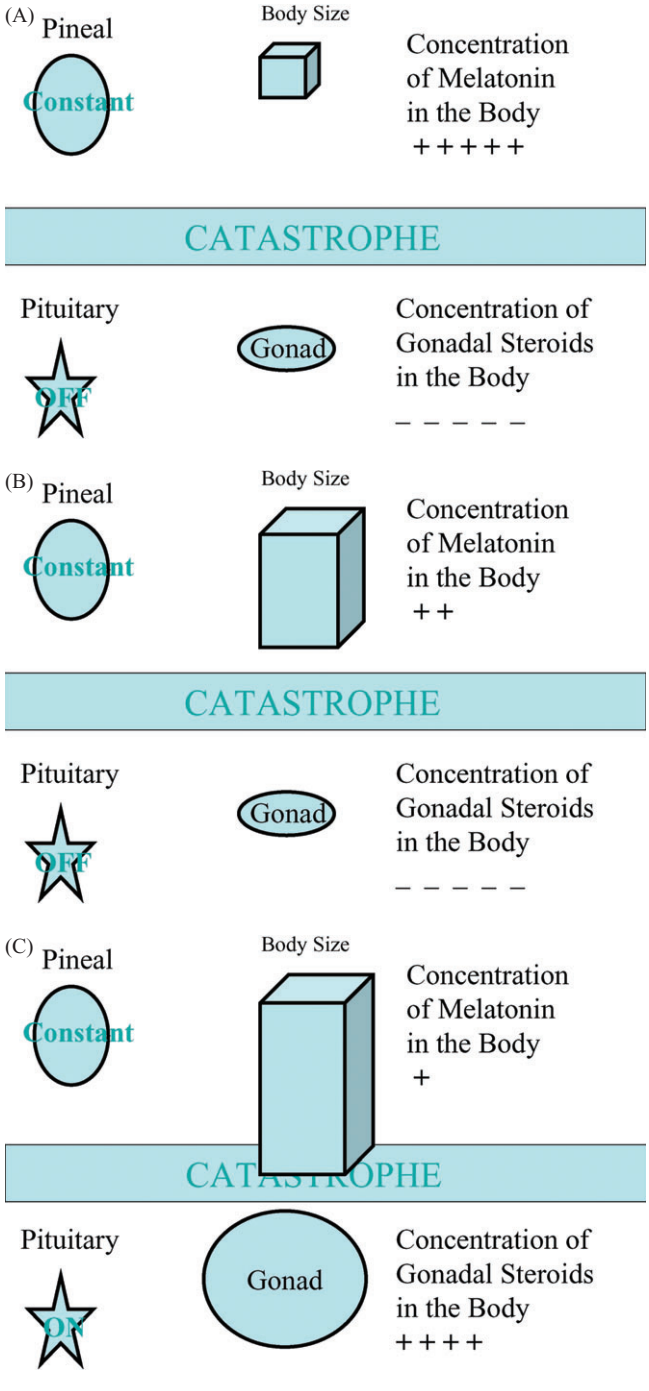

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Figure 5: A catastrophe model for the onset of puberty. (A) An infant. There is reduced body mass (small box, top centre). There is constant 24-hour output of melatonin from the pineal gland (sphere, top left). The consequence is (1) high levels of circulating melatonin (top right), leading to the inhibition of the hypothalamic gonadtrophin-releasing hormone (GnRH) pulse generator leading in turn to the inhibition of pituitary follicle-stimulating hormone (FSH)/luteinising hormone (LH) (bottom left), leading in turn to the inhibition of the gonadal sex hormones (bottom centre and bottom right). (B) A prepubescent child. There is increasing body mass (larger box top centre). There is constant 24-hour output of melatonin from the pineal gland (sphere, top left). The consequence is (1) lower levels of circulating melatonin (top right) but not low enough to activate the GnRH pulse generator. (C) A post-pubescent adolescent. There is a further increase in body mass (even larger box, top centre). There is constant 24-hour output of melatonin from the pineal gland (sphere, top left). The consequence is (1) a drop in the circulating concentration of melatonin (top right) to levels which are low enough to activate the hypothalamic GnRH pulse generator, leading in turn to the activation of pituitary FSH/LH (bottom left), leading in turn to the activation of the gonadal sex hormones (bottom centre and bottom right)

necessarily much higher in a 3-year old child than a 30-year old adult, because there is less body mass in which it is diluted (Young et al., 1988).

A 'catastrophe' explanation for the occurrence of puberty would then be the following: a) the constant daily output of melatonin from the pineal gland throughout life is in a state of disequilibrium with the increase in body mass during childhood; b) this disequilibrium causes the circulating concentration of melatonin to decrease as body mass increases; c) the moment of collision (catastrophe) occurs when the circulating melatonin concentration drops below a critical concentration, at about 10 years, d) permitting activation of the GnRH pulse generator; and e) creating the new homeostatic state of the post-pubescent adolescent (Figure 5A–C) (Silman, 1991).

Victory and defeat

So why are catastrophe and homeostasis the surrogates for revolution and counter-revolution? In Figure 1, the parallel is evident. Catastrophe stands in the place of revolution, because it is destined to overthrow the established order. It is a movement for change. Homeostasis stands in the place of counter revolution, because it seeks to protect the established order and maintain the status quo. And just as in 1968, when counter-revolution triumphed over revolution, so in science, homeostasis triumphs over catastrophe. Why? Because catastrophe is of little practical consequence for the scientist. Even if Paul and I have successfully contributed to an explanation of why change occurs, it changes nothing. Even if the GnRH pulse generator fails to turn on at puberty, it does not matter because medical intervention can make it occur therapeutically. Homeostasis, on the other hand, has immense practical significance. It leads directly to how disease – the disruption homeostasis – can be treated.

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By espousing the cause of catastrophe, Paul and I found ourselves once again on the losing side. Catastrophe is a transient moment of major change that is always supplanted by the re-imposition of a homeostatic order. A brief moment of revolution always gives place to a semi-permanent counter revolution. Our lives had come full circle.

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